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Mesenchymal stem cells in tumor development

Emerging roles and concepts

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Abbreviations: bFGF, basic fibroblast growth factor; CXCL_, C-X-C motif chemokine; CXCR_, C-X-C motif chemokine receptor; CCL_, C-C motif chemokine; CCR_, C-C motif chemokine receptor; CAF or TAF, cancer-associated fibroblast or tumor-associated fibroblast; EGF, epidermal growth factor; ETS, e-twenty-six family of transcription factors; GvHD, graft versus host disease; HDGF, hepatoma-derived growth factor; HSC, hematopoietic stem cell; IGF, insulin-like growth factor; IL-, interleukin; KGF, keratinocyte growth factor; LL-37, cathelicidin; MCP-1, monocyte chemotactic protein-1; MMP-2, matrix metalloproteinase-2; MSC, mesenchymal stem cell; PECAM-1, platelet endothelial cell adhesion molecule-1 (CD31); PDGF, platelet-derived growth factor; SDF-1, stromal-cell derived factor-1; TGFβ, transforming growth factor beta; uPA, urokinase plasminogen activator; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that participate in the structural and functional maintenance of connective tissues under normal homeostasis. They also act as trophic mediators during tissue repair, generating bioactive molecules that help in tissue regeneration following injury. MSCs serve comparable roles in cases of malignancy and are becoming increasingly appreciated as critical components of the tumor microenvironment. MSCs home to developing tumors with great affinity, where they exacerbate cancer cell proliferation, motility, invasion and metastasis, foster angiogenesis, promote tumor desmoplasia and suppress anti-tumor immune responses. These multifaceted roles emerge as a product of reciprocal interactions occurring between MSCs and cancer cells and serve to alter the tumor milieu, setting into motion a dynamic co-evolution of both tumor and stromal tissues that favors tumor progression. Here, we summarize our current knowledge about the involvement of MSCs in cancer pathogenesis and review accumulating evidence that have placed them at the center of the pro-malignant tumor stroma.

Introduction

The study of tumor pathogenesis has, for many years, largely focused on the accumulation of genetic or epigenetic alterations intrinsic to cancer cells, while almost entirely disregarding the vital contributions of the tumor stroma.[1] However, in the past decade or so, studies focused on understanding the complex crosstalk between cancer cells and the heterogeneous milieu of tumor stromal cells have allowed for an increased appreciation of the critical nature of some of these interactions, not only in supporting, but also in driving tumor growth and progression.[2]

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We now recognize that developing tumors can mobilize a variety of cell types from both local and distant niches via secreted chemical factors derived from the cancer cells themselves or from neighboring cells disrupted by a growing neoplasm.[3] These recruited cells significantly alter the composition of the tumor milieu and set into motion a complex series of interactions which result in the co-evolution of both cancer and stromal compartments.[4,5]

The stroma of solid cancers contains a variety of mesenchymal cell types, such as endothelial cells, lymphocytes, macrophages, neutrophils and cancer-associated fibroblasts, whose contributions to tumor development have now been extensively characterized and are the subjects of accompanying reviews in this Special Focus. More recently appreciated, however, are the contributions of a class of multipotent mesenchymal progenitor cells found to reside within the tumor microenvironment called mesenchymal stem cells (MSCs) (e.g., refs. 6–8). In the last few years, MSCs have been demonstrated to play important roles in tumor pathogenesis and are for this reason the subject of intense investigation.

MSCs are a heterogeneous class of self-renewing, multipotent progenitor cells that reside primarily in the bone marrow, but can also be found in a variety of other tissues throughout the body.[9-14] They display a number of remarkable properties, such as the tendency to home to sites of injury, the capacity to suppress immune reactions and the ability to aid in the repair and regeneration of damaged tissues.[15-17] Accordingly, MSCs have been explored widely for their applications in regenerative medicine and as delivery vehicles for use in gene therapy.[18]

In the context of cancer, MSCs are becoming increasingly recognized as important stromal facilitators of tumor development. Indeed, MSCs display avid tropism for developing tumors, akin to their abilities to home to wounded tissues[19] and are integral components of the cancer stroma in experimental as well as in clinical settings (e.g., refs. 6, 7 and 20–22). Furthermore, numerous studies have now demonstrated that human MSCs enhance tumor growth and/or metastatic progression in neoplasias arising from a wide range of tissues.[23-34] Although the specifics of the mechanisms by which MSCs enhance tumor progression and metastasis are only beginning to be understood, their reported influences can now be generally classified into four broad functional categories. First, MSCs within the tumor stroma may exert direct paracrine influences on the cancer cells, promoting tumor proliferation, invasion and metastasis (e.g., ref. 21). Second, tumor-associated MSCs may exert indirect pro-malignant actions by promoting tumor angiogenesis through recruitment of endothelial progenitor cells and by facilitating the formation and maturation of tumor vasculature (e.g., refs. 35 and 36). Third, by virtue of their progenitor status, MSCs may respond to the panoply of signals and cues present in the tumor microenvironment by differentiating into other types of stromal cells. For example, MSCs have been reported to differentiate into cancer-activated fibroblasts (CAFs), which can in turn influence tumor development.[37,38] Fourth, stromal MSCs may exert immunomodulatory properties that protect the tumor cells from detection and destruction by the adaptive immune system, functions that can be manifested through the direct or indirect actions of MSCs on various immune cells (reviewed in ref. 39). Because of these activities, MSCs are becoming increasingly accepted as important contributors to tumor progression, likely representing a critical component of the tumor-associated stroma. Here, we briefly expand on these themes and summarize recent efforts in elucidating the mechanisms by which these stromal stem cells contribute to tumor pathogenesis.

Identification and Characterization of MSCs

The initial characterization of MSCs dates to the observations of Friedenstein and colleagues, who cultured and propagated bone-marrow-derived non-hematopoietic cells that had the potential to give rise to bone and cartilage[40] (reviewed in ref. 41). These findings were reproduced by further studies in the subsequent years[42-48] and paved the way toward the definitive identification of multipotent stem cells within heterogeneous human MSC cultures.[41,49] These cells exhibited phenotypic properties that were unambiguously distinct from those of hematopoietic stem cells (HSCs) or endothelial progenitor cells.[50]

MSCs are classically characterized by their tri-lineage differentiation potential into osteoblasts, chondrocytes and adipocytes.[51,52] However, they also possess additional differentiation potentials and have been shown to give rise to myoblasts, endothelial cells, pericytes or fibroblasts and have more recently been reported to generate non-mesenchymal cells as well, such as epithelial cells, hepatocytes or even neuronal cells.[49,53-56] Phenotypically, they are plastic-adherent fibroblastic cells that express the cell surface antigens CD29, CD44, CD49, CD73, CD90, CD105, CD106, CD140b, CD166 and STRO-1, but lack key hematopoietic markers such as CD11b, CD14, CD19, CD31, CD34, CD45 and CD133.[52,57] Using these markers, researchers have been able to isolate MSCs or MSC-like cells from multiple tissues, including peripheral blood, adipose tissue, umbilical cord blood, fetal liver, lung, amniotic fluid, synovial fluid and gingival tissue.[9,13,14,58-61] Genotypically, MSCs derived from different tissue sources appear to exhibit different expression levels of the embryonic-stem-cell-associated pluripotency factors NANOG, OCT-4 and/or SOX2.[62,63] However, the functional contribution of such transcription factors to the proliferative and differentiation capacities of MSCs is still a matter of active debate (e.g., refs. 64 and 65).

MSCs in Wound Responses

MSCs play important roles in maintaining normal tissue homeostasis under resting conditions. These activities include the regulation of vital processes, such as hematopoiesis,[49,66,67] the preservation of blood vessel integrity[68] or bone maintenance.[69] More appreciated, however, are the functions of MSCs in cases of wound healing and tissue repair.[70] In these respects, current models suggest that MSCs are dispatched from their niches in response to systemic signals derived from injured tissues (e.g., ref. 71). The subsequent integration of the mobilized MSCs within these tissues is thought to provide an environment conducive to tissue rejuvenation and wound closure.

The "healing" functions of MSCs appear to be manifested via three key activities. First, an ability, by virtue of their plasticity, to differentiate on site to replenish tissues lost during injury. This is especially apparent in osteochondral disorders, where the differentiation of MSCs into chondrocytes or osteoblasts may, at least partly, contribute to the repair of these tissues (reviewed in ref. 48). Second, MSCs may exert their actions through the release of trophic factors that contribute to tissue regeneration by stimulating the activation of local tissue-specific stem cells. For instance, MSCs have been suggested to enhance the proliferation of local cardiac stem cells in heart infarction models.[72] Third and importantly, MSCs appear to promote immunosuppressive environments capable of inhibiting the functions of the adaptive immune system. In fact, MSCs cause the formation of T-regulatory cells (T-regs) in the context of inflammation[73] and have been shown to inhibit other aspects of immune cell functions, such as antibody release[74] and dendritic cell maturation.[75,76] While these aforementioned activities entail the local engraftment of MSCs in sites of wounding, new evidence indicates that MSCs may not even need to engraft locally at the wounded sites in order to enhance tissue repair, suggesting that they may also exert actions at a distance.[77-79]

Due to their increased avidity to wounds in experimental models, as well as their differentiation versatility, MSCs are being heavily explored for applications in regenerative medicine[80] and hold great clinical promise for the treatment of a number of diseases in a wide variety of tissues, including osteochondral diseases,[81,82] cardiovascular diseases,[83,84] liver disease,[85] renal diseases,[86] spinal cord injuries,[87] immunosuppression to benefit organ transplantion[88] and neurodegenerative diseases.[89,90]

MSC Homing to Tumors

Growing tumors continuously remodel local tissue architecture and generate chronic inflammatory responses similar to those evoked by open wounds.[19] Accordingly, it is believed that MSCs migrate into tumors in a manner similar to the way they migrate into injured tissues.[91] Indeed, MSCs introduced into the systemic circulation of tumor-bearing animals exhibit avid and preferential homing to cancerous growths, with limited homing to other tissues.[20,21] This preferential migration has now been convincingly demonstrated in a number of xenograft models, such as melanoma,[92] ovarian carcinoma,[93] breast carcinomas[21] and hepatocellular carcinomas[94] and has been described in detail using enhanced detection methods for tracking injected MSCs.[22] Importantly, endogenous MSCs have been recovered from the stroma of both experimental xenograft tumors[21] and human tumors,[6,7] suggesting that cancer development entails the continuous recruitment of MSCs, which may maintain steady-state levels within tumor stroma.

The prevalent model of MSC recruitment into tumors describes their mobilization from systemic niches, ostensibly in the bone marrow,[95] and their subsequent homing to cancer growths in response to chemotactic agents emitted by cancer cells. Although much remains to be proven about the molecular details underlying such a model, accumulating research has begun cataloging the molecules that control the avidity of MSCs to tumor sites. The list of soluble factors governing MSC recruitment to tumors is growing at a fast pace. Early on, due to the high affinity of HSCs and their leukocyte progeny for wound and tumor sites, investigators looked to the already well-characterized processes of HSC and leukocyte homing for clues driving MSC migration.[96,97] Indeed, factors involved in HSC and immunocyte recruitment, such as monocyte chemotactic protein-1 (MCP-1),[98] stromal-cell derived factor (SDF-1),[99] cyclophilin B and hepatoma-derived growth factor (HDGF),[100] urokinase plasminogen activator (uPA),[101,102] interleukin (IL-)6,[103] basic fibroblast growth factor (bFGF)[104] and vascular endothelial growth factor (VEGF)[104] have all been implicated in driving the tropism of bone-marrow-derived MSCs to tumors. It is believed that an active inflammatory response is necessary to allow MSC recruitment to tumor sites.[91] Many such factors, produced as a result of tissue damage or growing neoplasms, exhibit chemo-attractant properties toward MSCs in vitro and include bFGF,[105] VEGF,[106] platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) and variety of other growth factors such as transforming growth factor (TGFβ),[107] chemokines and cytokines,[108] cathelicidin (LL-37)[109] and even complement components C3a and C5a.[110] Non-neural cholinergic mediators[111] and dopamine derived from innervating sympathetic nerves have also recently been implicated in MSC homing to wound sites.[112] It is important to note, however, that the inhibition of the actions of any one single factor does not appear to be sufficient to completely disrupt MSC homing to tumors, suggesting that multiple concerted mechanisms cooperate in regulating their tropism to tumor growths.[113]

MSCs derived from non-bone-marrow sources also possess the abilities to home to tumors and appear to respond to chemotactic signals emitted by cancer cells just as well as bone-marrow-derived MSCs. For example, umbilical-cord-derived MSCs home to medulloblastoma cells in response to matrix metalloproteases (MMP)-2[99] and adipose-derived stromal cells can contribute to the malignancy of cancer cell lines derived from a number of different tissues.[26-29,114] These observations challenge the current dogma that tumor-associated MSCs are derived solely from bone marrow sources and raise the notion that other MSC-rich tissues (such as adipose tissue) may also contribute to the pools of certain tumor stromal MSCs.

A critical component of the homing of MSCs to cancer sites is their ability to execute transmigration through the endothelial cells of the vessel wall. How MSCs interact specifically with endothelial cells is an area that is receiving a lot of attention and is starting to be illuminated with increasing molecular clarity. The identification of the adhesion molecules and surface receptors that guide the vascular adhesion of MSCs has been aided by comparisons to the similar activities of HSCs and leukocytes (reviewed in ref. 115). Like hematopoietic cells, MSCs appear to utilize E-selectin for vascular adhesion, but lack other hematopoietic cell adhesion molecules such as L-selectin, β2 integrins and platelet endothelial cell adhesion molecule-1 (PECAM-1)/CD34 that facilitate the rolling of HSCs on vasculature and their subsequent transmigration through the endothelial wall.[116] Alternatively, other sets of adhesion molecules, such as endothelial-cell-expressed P-selectin, which can interact with CD44 on the surface of MSCs,[117] or vascular cell adhesion molecule-1 (VCAM-1),[118] C3a, C5a[110] and C-X-C motif chemokine 5 (CXCL5)[119] have all been shown to be important for MSC extravasation across endothelial barriers. Finally, a prominent mechanism reported to control the efficiency of transendothelial migration of MSCs is shear stress. Indeed, low-shear conditions cause the downregulation of certain chemokine receptors, such as C-X-C motif chemokine receptors (CXCR) 3 and 6 and C-C chemokine receptors (CCR) 6 and 9 in cells crossing the aortic endothelial barrier,[120] while high shear-stress conditions appear to cause the upregulation of integrins in MSCs adhering on endothelial ligands.[116]

While the specifics regarding MSC homing to tumor sites are still being investigated, new evidence suggests that stromal cells also participate in MSC recruitment into tumors. For example, cancer-associated fibroblasts (CAFs) reported to be derived from MSCs in the context of gastric cancers have been shown to further recruit primitive MSCs from the bone marrow via the secretion of SDF-1.[37,38] This raises the notion that the homing and integration of MSCs into tumors may initiate a vicious cycle, causing further recruitment of MSCs, thereby maintaining their numbers in tumor stroma and sustaining their contributions to tumor pathogenesis.

MSCs in Tumor Pathogenesis

The contributions of tumor-associated MSCs to cancer development have been the subject of intense investigations. While certain studies suggest that MSCs play tumor-suppressive roles (e.g., ref. 121), they are outnumbered by an overwhelming literature that has incriminated MSCs in serving tumor-promoting functions and in a wide range of cancer models. Indeed, MSCs have now been demonstrated to serve pro-malignant roles in a number of epithelial cancer subtypes, such as breast,[21,27] colon,[25,30] lung,[26,32] skin[23,24,29] or prostate.[28,31] MSCs have also been shown to drive hematopoietic malignancies, such as multiple myeloma,[122,123] and appear to sustain leukemia/lymphoma development.[124] Finally, MSCs have recently been found to promote the progression of certain mesenchymal cancers as well, such as osteosarcomas, which are thought themselves to arise, in part, from the neoplastic transformation of MSC lineages[34] (discussed in more detail below).

As their roles in tumor pathogenesis are still being characterized in detail, several major mechanisms through which MSCs contribute to tumor development are emerging. First, MSCs exert direct actions on the cancer cells through the secretion of a variety of bioactive molecules whose paracrine actions influence the phenotype of the cancer cells. Second, the immunosuppressive properties of MSCs, as described above, alter the local composition of immunocytes and derail immune reactions that are mounted against malignant cells, therefore providing an immune-privileged environment for neoplastic cells. Third, MSCs can influence tumor vascularization by exacerbating tumor angiogenesis. Fourth and finally, as progenitor cells, tumor-associated MSCs have been reported to differentiate within the tumor microenvironment and act as local sources for other tumor stromal cells, such as tumor-associated fibroblasts (TAFs). In the following sections, we will summarize the current knowledge pertaining to each of these mechanisms and explore in more detail the varied functions of tumor-associated MSCs in tumor biology.

Direct actions of MSCs on cancer cells. MSCs produce a plethora of molecules, such as chemokines, cytokines and growth factors, which act in a paracrine fashion on their respective receptors on the surface of cancer cells, thereby regulating tumor growth and/or progression. For example, MSC-derived chemokines, such as CXCL1, CXCL2 or CXCL12/SDF-1, have been shown to foster cancer cell proliferation in a number of cancer models via their actions on their respective CXCR2 and CXCR4 receptors on cancer cells.[125,126] Similarly, cytokines secreted by MSCs, which include IL-6 and IL-8, have been demonstrated to enhance cancer cell malignancy in the context of several cancers, such as breast[6] or colorectal.[127] Finally, MSC-derived growth factors, such as epidermal growth factor (EGF), act on their cognate receptors on the surface of cancer cells, enhancing tumorigenesis in the setting of breast cancer.[8]

While the list of MSC-derived peptide messengers is expanding, it is important to note that MSCs can also provide additional agents/materials that can act on the cancer cells in a paracrine fashion. In these respects, new research suggests that nucleic acids are effectively transferred from MSCs to cancer cells, potentially via mRNA- and/or microRNA-rich microvesicles[128] or through gap junctions established following physical interactions between the two cell types.[129] These observations suggest that cancer cells effectively respond to the innate abilities of MSCs to produce and secrete a rich and vast array of bioactive molecules that can influence the course of tumor development.

In concert with the rich set of bioactive molecules they "normally" generate, MSCs respond to the contextual signals emanating from the cancer cells in their microenvironment by initiating de novo secretion of soluble factors that impact tumor pathogenesis.[21] Of note in this regard is the de novo ability of MSCs to produce the chemokine CCL5 upon stimulation by breast cancer cells.[21] Here, CCL5 mRNA levels (and subsequently protein levels as well) in the MSCs are induced by > 1,000 times upon their physical contact with the cancer cells. CCL5 then acts in a paracrine fashion on the cancer cells, fostering metastasis by increasing their ability to extravasate into lung parenchyma in experimental models.[21] Interestingly, not all cancer cells possessed the ability to instigate CCL5 from the MSCs, lending credence to the notion that idiosyncratic differences exist between cancer cells (and the way in which they respond to interactions with MSCs) even within the same tumor subtype. Similarly, the interaction of MSCs with lung cancer cell lines was found to cause stanniocalcin-1 (STC-1) secretion by the activated MSCs, which in turn upregulates uncoupling protein 2 to protect the neighboring cancer cells from ROS-induced apoptosis.[130,131] Taken together, these findings raise the notion that contextual signals control the manner of MSC activation and, accordingly, may regulate their functions within the tumor microenvironment (discussed in more detail below).

The transcriptional, secretory and phenotypic changes induced in MSCs following their interactions with cancer cells likely underlie some of the tumor-beneficial effects they potentiate while contributing to the dynamic evolution of the tumor stroma. However, it is important to note that cancer cells also undergo phenotypic and transcriptional changes as a result of their interactions with MSCs. A gamut of different MSC-instigated signal transduction pathways have been studied and they regulate vital machineries in the cancer cells, such as cell cycle/proliferation,[8,125,129] but also several phenotypes associated with malignancy, such as motility,[21,125,126,132] invasion[21,133] and metastasis.[21,27,30,134]

In this regard, three important MSC-fostered cancer phenotypes deserve particular mention: (1) the ability of MSCs to regulate cancer stem cells (CSCs)—cells with increased tumor-initiating abilities (reviewed in ref. 135), (2) their ability to enhance the resistance of cancer cells to chemotherapy and (3) the ability of MSCs to drive the metastatic predilection of cancer cells to certain tissues, such as the bone. Indeed, recent studies have found that labeled human MSCs injected into mouse tibias homed to sites of growing orthotopic breast cancer xenografts and increased the population of cancer stem cells (CSCs) via the paracrine actions of IL-6 and CXCL7.[6] Similarly, tumor-associated MSCs were found to enhance the generation of cancer stem cells in ovarian carcinoma, in this case, via BMP2 signaling.[7] Along similar lines, MSCs have been described to play a role in cancer-cell-resistance to classical chemotherapy. For example, MSCs were found to protect lung cancer cells from apoptosis as a result of oxidative or chemotherapeutic stress.[130] Furthermore, endogenous human MSCs were found to protect tumor cells against chemotherapeutic agents by secreting chemoprotectant polyunsaturated fatty acids in response to activation by platinum analog,[136] an action they exert at a distance, without the need to engraft within tumors. Finally, strong evidence suggests that MSCs may preferentially drive tumor metastasis to the bone (e.g., ref. 137), through mechanisms that involve, in part, MSC-derived IL17BR.[33] Although the molecular underpinnings of the abilities of MSCs to regulate these three phenotypes have not been fully determined, some evidence suggests that the mechanisms underlying such activities may at least be interrelated. Indeed, CSCs and cancer cells resident in bone exhibit increased resistance to chemotherapy and are refractory to tumor irradiation.[138]

Immunosuppressive properties of MSCs. MSCs act as immune modulators with reported activities in suppressing both innate and adaptive immune responses (reviewed in refs. 77 and 139). Indeed, their ability to quell the immune system is so potent, it has been exploited to reduce the severity of graft vs. host disease (GvHD).[140-142] MSCs appear to modulate immune responses via differential influences they exert on the proliferative capacities of immune cells. For example, MSCs inhibit the proliferation and maturation of B-cells[74] as well as natural killer cells,[143-145] while exhibiting protective activities toward other cells, such as neutrophils.[146] In similar respects, MSCs have been shown to directly inhibit both $CD4^+$ and $CD8^+$ T-cell proliferation,[147] suggesting that MSCs can influence the behavior of almost all of the key immune activities involved in tumor development.

The exact molecular details of how MSCs exert these immunomodulatory functions are only partially characterized. Several mechanisms of action appear to involve their innate or stimulated abilities to secrete cytokines and chemokines, which suppress immune cell proliferation or activation.[77,148] For example, MSC-derived interferon-gamma was found to be sufficient in suppressing T-cell effector functions in a number of settings.[149] Furthermore, stimulation of Toll-like receptor (TLR)-3 and -4 present on the surface of MSCs leads to the production of IL-6, IL-8 and CXCL10, which were critical for the suppression of T-cell proliferation.[150] MSCs may also indirectly quell T-cell proliferation by influencing dendritic cell (DC) proliferation and maturation.[75,76,151-153] This is accomplished, in part, by MSCs driving DC differentiation into a subtype incapable of stimulating T-cell expansion.[148]

Finally and perhaps most importantly, MSCs can direct T-cells to differentiate into T-reg, which, in the case of tumors, can confer growth and metastatic advantages.[139,154,155] These advantages are manifested through T-reg-mediated suppression of normal innate and adaptive immune responses, including the direct inactivation of effector T-cells and NK cells (reviewed in ref. 156). Although the mechanisms underlying the MSC mediated generation of T-regs is still under investigation, this process appears to involve MSC-secreted TGFβ1.[157] Taken together the immune-suppressive effects of MSCs are rather extensive and perhaps unrivaled by any other stromal cell type and constitute crucial protective mechanisms by which MSCs contribute to tumor growth and progression.

MSCs in tumor angiogenesis. MSCs play multifaceted roles in fostering tissue revascularization after injury and appear to serve similar pro-angiogenic functions in the setting of tumor development (reviewed in ref. 158). Indeed, MSCs (or their reported progeny; discussed below) may promote tumor neoangiogenesis via the secretion/production of angiogenic factors, such as VEGF-A, angiopoietins, EGF, keratinocyte growth factor (KGF), IGF-1 and galectin-1[159,160] and are involved in the recruitment of endothelial cells and in promoting the maturation of newly-formed blood vessels (e.g., refs. 32 and 161). Furthermore, MSCs themselves have been shown to be able to differentiate into endothelial-like cells and share cell surface markers with pericytes, thereby modulating the tumor vasculature.[162,163] Conversely, vascular endothelial cells have been recently reported to convert into cells with characteristic properties of MSCs,[164] suggesting that endothelial-to-mesenchymal or mesenchymal-to-endothelial transformations may be possible in the context of tumorigenesis. These observations highlight important roles for MSCs in supporting tumor vascularization and suggest that targeting MSCs may be a viable avenue in anti-angiogenesis-based cancer therapy.

MSCs as progenitors for tumor stroma. As mentioned above, the crosstalk operating between cancer cells and tumor-associated MSCs changes not only the cancer cells, but the MSCs as well. In these respects, the tumor microenvironment may affect, in addition to the properties of tumor-associated MSCs, their differentiation capacities. In fact, some evidence suggests that MSCs trans-differentiate within tumors to give rise to cancer associated fibroblasts (CAFs; see refs. 165 and 166).

CAFs have been increasingly appreciated in the last ten years as the importance of the stroma in tumor development has become more evident (e.g., refs. 167 and 168). They have been associated with poor patient prognosis[169,170] and are implicated in serving a multitude of pro-malignant activities, including, for example, the ability to enhance angiogenesis and to foster ECM remodeling (reviewed in ref. 171). The notion that MSCs generate CAF populations is highly interesting and holds the potential of shedding much needed light on the origin(s) of CAFs and on the fate of MSCs once recruited into the tumor microenvironment. A cautionary note, however, is that much of the markers associated with CAFs (such as SMA) are already present, to a certain extent, in the MSC populations. Accordingly, it remains to be determined whether the described conversion of MSCs to CAFs is due to the selection of pre-existing cells (e.g., by TGFβ[165]) or whether it results from the bona fide stable differentiation of MSCs into CAFs. Improved and unique functional determinations for the CAF phenotype, along with improved and unique markers characterizing MSCs will be instrumental in clarifying the potential inter-relationship of CAFs to MSCs.

MSCs as Cells-of-Origin for Cancer

MSCs may represent the cell-of-origin for certain sarcomas, such as Ewing's family sarcomas (reviewed in ref. 172). Indeed, a number of observations suggested that the expression of the fusion product between FLI-1 (a member of the E-26 family of transcription factors or ETS genes) and the EWS DNA-binding domain, can cause the transformation of MSCs into Ewing sarcoma cells.[173] First, established sarcoma lines in which EWS-FLI-1 was silenced reverted back to a transcriptional program resembling that of MSCs.[174] Second, revertants regained a progenitor status and were capable of differentiating into osteoblasts and adipocytes, corroborating their origins as MSCs. Third, this activity appears to be restricted to the highly tumorigenic cancer-stem-cell-rich CD133-positive sarcoma cells, which expresses a series of stem-cell-associated genes, such as NANOG and OCT-4.[175] Along the same lines, the transformation of human MSCs by ectopic expression of other sarcoma-associated oncogenes, such as the synovial sarcoma translocated gene product (SYT-SSX1) or the FUS-CHOP gene product, generated cells with the ability to form synovial sarcomas[176] or myxoid liposarcomas,[177] respectively. Together, these observations suggest that MSCs may very well lie at the origin of multiple sarcomas and that they may be the targets of oncogenic transformation in human disease.

It is noteworthy to add that MSCs have also been directly incriminated in initiating epithelial cancers. Of note is the report by Houghton and colleagues who showed that bone-marrow-derived MSCs initiate gastric cancers by fusing with mucosal cells in a setting of *Helicobacter pylori* infection.[178] Whether MSCs also give rise to other cancers is yet undetermined.

Final Notes and Future Perspectives

The involvement of MSCs in tumor biology has attracted increased attention as of late and the knowledge regarding their biological attributes, their influence on cancer cells and their roles in human cancer pathogenesis is mounting at a fast pace. With this renewed interest comes the promise that such ongoing efforts will bring forth further insights into the still-enigmatic biology of these progenitor cells and the manners with which they impact human cancer development.

In these regards, some of the most important questions pertain to the origin(s) of tumor-associated MSCs. Indeed, whether tumor-associated stromal MSCs derive primarily from bone marrow niches or whether they arrive just as frequently from local reservoirs (similar in many ways to bone-marrow- and tissue-resident pools of hematopoietic stem/progenitor cells) is still unaddressed. This is of particular interest as MSCs derived from different sources do display some differences in the detailed

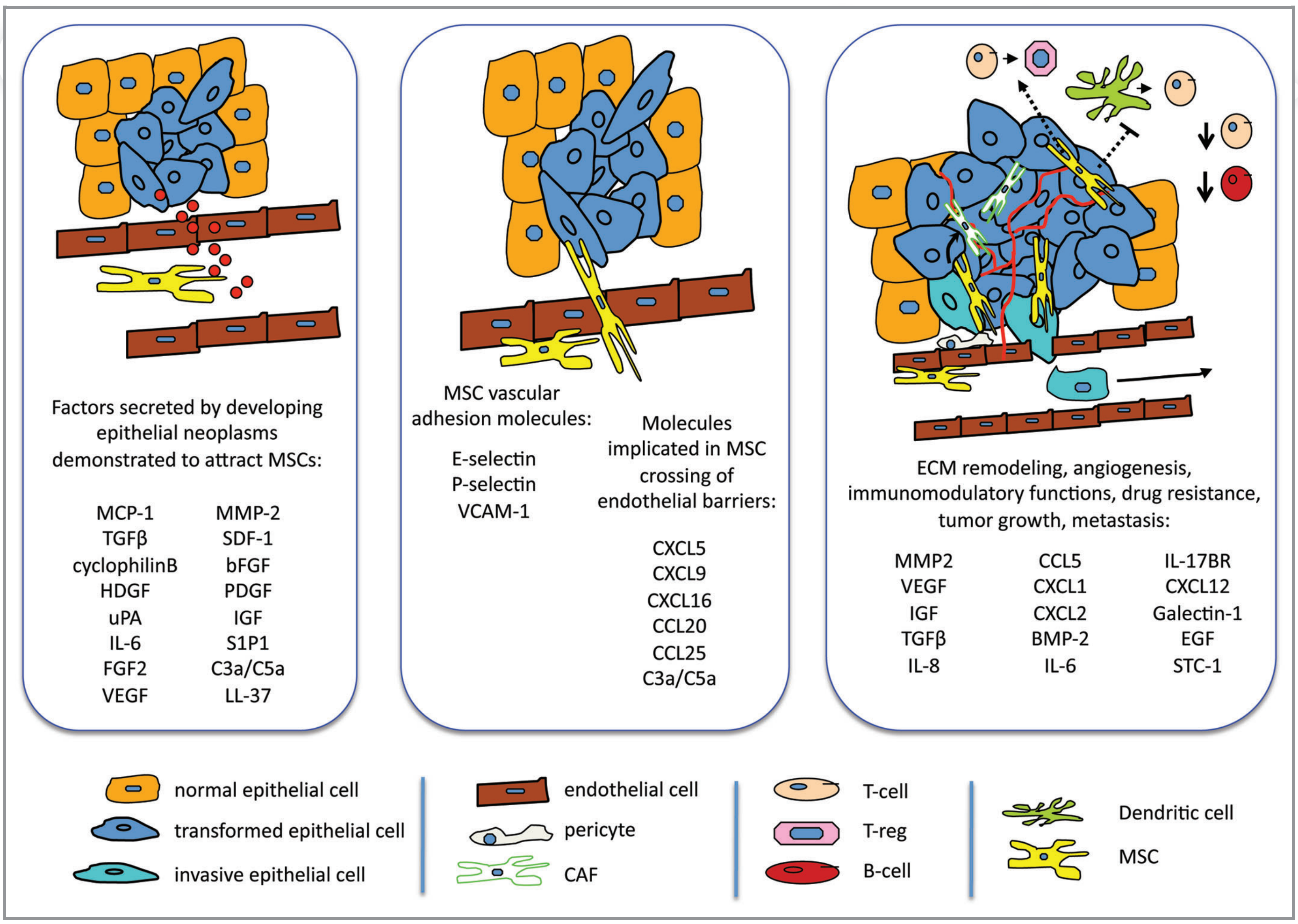

Figure 1. MSCs in tumor pathogenesis. Initial systemic factors released by tumor cells or by the disrupted surrounding tissues cause MSC mobilization and recruitment into tumors; MSCs cross vessel walls and home into cancers. MSC-derived trophic factors, including growth factors, chemokines and cytokines influence cancer cell phenotypes. The crosstalk between MSCs and cancer cells fosters remodeling of the tumor microenvironment and impacts other stromal cell types, including immune cells, enhances angiogenesis and/or permeabilization of the vasculature, causes cancer cell growth, local invasion and metastasis. Systemic factors derived from these interactions may influence distal sites/tissues, including secondary colonization sites.

mechanisms through which they support tumor development. Accordingly, the possibility that tumors may harbor MSCs derived from different anatomical origins raises the notion of whether these stromal stem cells contribute to tumor heterogeneity by fostering the evolution of cancer cells they come in contact with along different molecular paths.

Two additional important and interrelated questions that remain to be fully addressed are the degree of plasticity of MSCs once present in the tumor microenvironment and the lack of unique markers with which to distinguish them apart from other stromal cells within tumors. Although increased attention is now focused on the involvement of MSCs in tumor pathogenesis, the field is still complicated by the disparate methodologies still used across many labs to isolate MSCs from (healthy) donors, which contribute to such isolates being invariably different from one another across labs and clinics. The identification of unique MSC markers would, ostensibly, enable researchers to more uniformly determine the differentiation/stem states of MSC preparations derived from different tissues and importantly, would permit the attribution of their influences on tumor initiation and progression to the respective representation of such differentiated and/or stem cells within the original cultures. An attempt at placing a hierarchical relation between different MSCs has been performed recently and has proven to bear functional consequences on tumor development.[5]

In closing, MSCs appear to reside at the center of a complex crosstalk of interactions that drive the co-evolution of non-transformed stromal cells and neoplastic cells alike. These pathways now include a mounting number of interacting players and processes, summarized in **Figure 1**. The critical players essential for this crosstalk are only just beginning to be identified and have already been shown to control key features of cancer malignancy, such as stemness and metastasis. As they are, novel and beneficial anti-neoplastic approaches based on interdicting the crosstalk between MSCs and cancer cells will undoubtedly emerge.

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